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JC07 Rec'd PCT/PTO 10 DEC 2001

FORM PTO-1390 (Modified) (REV 5-93) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **065691-0261**

U S APPLICATION NO (If known, see 37 CFR 1.5): **Unassigned** 10/009341

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/01573	**06/08/2000**	**06/09/1999**

TITLE OF INVENTION
MORPHINE SULFATE MICROGRANULES, METHOD FOR PREPARING SAME AND COMPOSITIONS CONTAINING SAME

APPLICANT(S) FOR DO/EO/US
Dominique MARECHAL, Pascal SUPLIE and Pascal OURY

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☒ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau)
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made, however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. ☐ Applicant claims small entity status under 37 CFR 1.27 .

Items 12. to 17. below concern other document(s) or information included:

12. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3 28 and 3.31 is included
14. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ Other items or information:

JC07 Rec'd PCT/PTO 10 DEC 2001

U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Unassigned 10/009341	PCT/FR00/01573	065691-0261

18. ☒The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO $890.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 30 Months from the earliest claimed priority date (37 CFR 1.492(e))	$130.00	

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate		
Total Claims	10	-	20	=	0	×	$18.00	$0.00	
Independent Claims	1	-	3	=	0	×	$84.00	$0.00	
Multiple dependent claim(s) (if applicable)							$280.00	$0.00	
TOTAL OF ABOVE CALCULATIONS =								$890.00	
Reduction by ½ for filing by small entity, if applicable.								$0.00	
SUBTOTAL =								$890.00	
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +								$0.00	
TOTAL NATIONAL FEE =								$890.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +								$0.00	
TOTAL FEES ENCLOSED =								$890.00	
							Amount to be: refunded	$	
							charged	$	

a. ☒ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $_____ to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Customer Number: 22428

22428

22428

PATENT TRADEMARK OFFICE

SIGNATURE

NAME STEPHEN B. MAEBIUS

REGISTRATION NUMBER 35,264

Atty. Dkt. No. 065691/0261

#3/a

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Dominique Marechal et al.

Entitled: Morphine Sulfate Microgranules, Method for Preparing Same and Compositions Containing Same

Serial No.: To be assigned

Date Filed: Concurrently

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the present application, Applicants respectfully request that the above-identified application be amended as follows:

In the Claims:

In accordance with 37 C.F.R. § 1.121(c) (3), please substitute for pending claims 3-10 with the following clean version of the claims. The changes to these claims are shown explicitly in the attached "Marked Up Version of Claims."

3. (Amended) Microgranules according to claim 1, characterized in that the acrylic copolymer represents advantageously 5 to 15% by weight of the microgranules.

4. (Amended) Microgranules according to claim 1, characterized in that the neutral support grain coated with the active layer contains 40% to 50% of morphine sulphate and 10 to 20% of a pharmaceutically acceptable binder.

5. (Amended) Microgranules according to claim 1, characterized in that the sustained-release layer contains a plasticizer such as triethylcitrate and a lubricant.

6. (Amended) Microgranules according to claim 4, characterized in that their composition is as follows:

Morphine sulphate	30 - 40	%
Neutral support grain	30 - 40	%
Binder	10 - 20	%
Methacrylic acid copolymer	5 - 15	%
Plasticizer	1 - 2.5	%
Lubricant	2 - 4	%
Hydrophobic silica	0.2- 1	%

7. (Amended) Microgranules according to claim 1, characterized in that the relative mass proportion of the morphine sulphate and of the neutral support grain is between 40/60 and 60/40.

8. (Amended) Microgranules according to claim 1, characterized in that the morphine sulphate represents 30 to 40% by mass of the microgranules.

9. (Amended) Process for preparing the microgranules according to claim 1, characterized in that the active layer and the sustained-release layer are applied onto the neutral grains by emplcing in aqueous solution.

10. (Amended) Pharmaceutical composition containing the microgranules according to claim 1 optionally obtained according to the process for preparing the microgranules, characterized in that the active layer and the sustained-release layer are applied onto the neutral grains by emplacing in aqueous solution.

Atty. Dkt. No. 065691/0261

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application.

Respectfully submitted,

Date Dec. 10, 2001

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MARKED UP VERSION OF AMENDED CLAIMS

3. (Amended) Microgranules according to [one of the preceding claims] claim 1, characterized in that the acrylic copolymer represents advantageously 5 to 15% by weight of the microgranules.

4. (Amended) Microgranules according to [one of Claims 1 to 3] claim 1, characterized in that the neutral support grain coated with the active layer contains 40% to 50% of morphine sulphate and 10 to 20% of a pharmaceutically acceptable binder.

5. (Amended) Microgranules according to [one of Claims 1 to 4] claim 1, characterized in that the sustained-release layer contains a plasticizer such as triethylcitrate and a lubricant.

6. (Amended) Microgranules according to [Claims 4 and 5] claim 4, characterized in that their composition is as follows:

Morphine sulphate	30 - 40	%
Neutral support grain	30 - 40	%
Binder	10 - 20	%
Methacrylic acid copolymer	5 - 15	%
Plasticizer	1 - 2.5	%
Lubricant	2 - 4	%
Hydrophobic silica	0.2- 1	%

7. (Amended) Microgranules according to [one of the preceding claims] claim 1, characterized in that the relative mass proportion of the morphine sulphate and of the neutral support grain is between 40/60 and 60/40.

8. (Amended) Microgranules according to [one of the preceding claims] claim 1, characterized in that the morphine sulphate represents 30 to 40% by mass of the microgranules.

9. (Amended) Process for preparing the microgranules according to [one of Claims 1 to 8] claim 1, characterized in that the active layer and the sustained-release layer are applied onto the neutral grains by emplacing in aqueous solution.

10. (Amended) Pharmaceutical composition containing the microgranules according to [one of Claims 1 to 8] claim 1 optionally obtained according to the process [of Claim 9] for preparing the microgranules, characterized in that the active layer and the sustained-release layer are applied onto the neutral grains by emplacing in aqueous solution.

The present invention concerns a novel sustained-release morphine sulphate formulation for oral administration.

The present invention also applies to the process for manufacturing this formulation and to the pharmaceutical preparations containing it.

In the present application, "morphine sulphate" is intended to mean the sulphate salt, optionally hydrated, of (5 alpha, 6 alpha)-7,8-didehydro-4,5-epoxy-17-methylmorphinane-3,6-diol.

The oral administration of morphine sulphate is the best suited treatment for relieving chronic pain. Many oral formulations of morphine sulphate have been described in the prior art.

EP 205 282 (EUROCELTIQUE) relates to granules comprising morphine sulphate, an aliphatic alcohol and a water-soluble hydroxyalkylcellulose.

These granules are coated with a derivative of mucoadhesive cellulose, such as hydroxypropylmethyl-cellulose, and present a release profile over 12 hours, with a plasmatic peak situated between 1 and 3 hours.

EP 377 518 (FAULDING) discloses sustained-release granules containing a very water-soluble active principle such as morphine. The granules make it possible to maintain plasmatic levels higher than 75% of the maximum for at least 3 hours.

These granules comprise an active core coated with a polymeric layer which allows a slow release of the active principle at a very acid pH and a constant faster release of the active principle at a pH which is less acid to basic, over an extended period of time.

This polymeric layer contains three compounds: a polymeric matrix which is insoluble whatever the pH, an enteric polymer, the solubility of which is pH-dependent, and a polymer which is soluble in acid medium.

The preparations described in EP 377 518 have a bioavailability requiring an administration which should be at least twice daily.

A subject of EP 553 392 (EUROCELTIQUE) is a process for preparing a stable sustained-release formulation consisting of granules obtained in a fluidized air bed by spraying an aqueous solution of active principle over neutral grains, followed by a coating with HPMC, by a coating with an acrylic polymer and by a protective film required for reducing the agglomeration of the granules.

EP 636 366 (EUROCELTIQUE) discloses sustained-release morphine sulphate microgranules comprising a neutral core coated with an active layer consisting of an active principle/HPMC mixture, of a sustained-release layer consisting of Eudragit® RS D and/or of Eudragit® RL D, and of an HPMC film, which represents 5% of gain in mass.

In documents EP 533 392 and EP 636 366, the granules undergo a heat treatment above the glass transition temperature of the polymeric coating, in order to stabilize its structure. This heat treatment is carried out at 45°C approximately for at least 24 hours, which considerably lengthens the duration of the process.

EP 647 448 (EUROCELTIQUE) discloses morphine sulphate granules, the in vitro dissolution profile of which stretches over 24 hours. The granules consist of Neutral grains coated with active principle and with lactose. The active layer is covered with a film of Opadry®, and then coated with Aquacoat ECD 30®, Eudragit RS 30 D® or a Eudragit RS®/Eudragit RL® mixture: 97.5/2.5. The titre of the granules described in this document is quite low, of the order of 15%.

US 5,445,829 (KV Pharmaceutical) relates to a formulation which is capable of releasing the active principle exclusively between 12 and 24 hours after the administration.

This formulation contains 0 to 50% of immediate particles and the complement of controlled-release particles consisting of immediate particles coated with a cellulose derivative as delaying polymer.

WO 94/22431 (KAPIPHARMACIA) discloses a controlled-release formulation of a morphine salt.

This formulation can be administered in a single daily dosage intake. At 32 hours, the plasma concentration is higher than Cmax/2 and the fluctuations in the release profile are very small over this period, and so the plasmatic concentration is virtually constant over 24 hours.

The formulation disclosed in WO 94/22431 consists, for example, of granules containing a core of morphine salt, of lactose and of a binder, coated with a film of HPMC/EC and of triethyl citrate.

This formulation uses a mixture of two polymers, one being soluble and the other being insoluble in water.

WO 95/31972 (EUROCELTIQUE) discloses sustained-release morphine sulphate granules consisting of a neutral core coated with active principle and with hydrated lactose, the bulk density of which is between 0.4 and 0.9 g/ml. The delayed-release layer coating the active principle contains for example an acrylic polymer, an alkylcellulose, a hydrogenated vegetable oil or a mixture thereof.

This document teaches that the binding of the morphine sulphate to the neutral cores requires the addition of the lactose as a diluent.

The release profiles of the microgranules given by way of example show that these granules are suitable for one dosage intake per day.

WO 96/14059 (EUROCELTIQUE) discloses a process for extruding spherical particles containing morphine sulphate, a support the melting point of which is between 35 and 150°C and a sustained-release agent.

The support is a hydrogenated vegetable oil or a PEG (Mw 1000 to 20,000). The in vitro dissolution profile of these particles is 67% at 24 hours. No in vitro result is provided.

WO/960066 (ALZA) describes a composition containing morphine sulphate, polyvinylpyrrolidone and a polyalkylene oxide.

This document claims that the formulation provides a sustained release over time, but gives no example either in vitro or in vivo, and so it is difficult, upon reading the document, to estimate whether the administration should be one or more dosage intakes per day.

The subject of the present invention concerns sustained-release morphine sulphate microgranules each comprising a neutral support grain coated with an active layer and with a sustained-release layer, characterized in that the sustained-release layer contains a copolymer of methacrylic acid and of methyl methacrylate ester, the relative proportion of the free carboxyl groups and of the ester groups of which is equal to 0.5 approximately, and a silica exhibiting a hydrophobic nature.

The hydrophobic silica represents advantageously 0.2 to 1% by weight of the microgranules. Aerosil® R 972 is preferred as hydrophobic silica.

The microgranules of the invention exhibit in particular the advantage of lacking a protective film coating the sustained-release layer. In addition, it is not necessary to subject the microgranules to a very lengthy heat treatment (longer than 24 hours) as in the prior art to improve the structure of the sustained-release layer.

The acrylic copolymer represents advantageously 5 to 15% by weight of the microgranules.

The relative mass proportion of the morphine sulphate and of the neutral support grain is preferably between 40/60 and 60/40.

The morphine sulphate represents advantageously 30 to 40% by mass of the microgranules.

The neutral support grain coated with the active layer contains preferably 40% to 50% of morphine

sulphate and 10 to 20% of a pharmaceutically acceptable binder.

The sustained-release layer contains preferably a plasticizer and a lubricant. The plasticizer and the lubricant are chosen from the pharmaceutically acceptable plasticizers and lubricants which are well known to persons skilled in the art. The plasticizer is for example triethylcitrate.

The composition of the microgranules according to the invention is advantageously as follows:

Morphine sulphate	30 - 40	%
Neutral support grain	30 - 40	%
Binder	10 - 20	%
Methacrylic acid copolymer	5 - 15	%
Plasticizer	1 - 2.5	%
Lubricant	2 - 4	%
Hydrophobic silica	0.2- 1	%

The neutral support grains have a particle size of between 200 and 1000 µm, preferably of between 400 and 600 µm.

The present invention also concerns a process for preparing the microgranules described above. This process is carried out entirely in aqueous medium. It comprises a step of emplacing, in aqueous solution, the active principle on neutral support grains and a step of coating with a methacrylic copolymer, still in aqueous solution.

The granules are advantageously prepared in a perforated rotary turbomixer or a fluidized air bed. The spraying of the emplacing and coating solutions and/or suspensions is preferably continuous and followed by a drying step at a temperature of between 30 and 65°C.

It is not necessary for the granules according to the invention to undergo a heat treatment for the structure of the film to be satisfactory.

The present invention finally concerns the pharmaceutical compositions containing the

microgranules of the invention optionally obtained according to the process described above.

The following examples illustrate the invention without limiting the scope thereof.

The percentages are expressed by weight.

The figure represents the mean of the in vitro dissolution profile of four formulations according to the invention (curves 1, 2, 3 and 4). The percentage of dissolution is on the x-axis and the time (hours) on the y-axis.

Example 1 (Batch A)

- **Preparation of the granules**

An emplacing solution containing 74.7% of purified water, 6.6% of Pharmacoat 603® (hydroxypropylmethylcellulose) and 18.7% of morphine sulphate is prepared. Stirring is maintained until the solution is homogeneous, and then throughout the emplacing.

Neutral support grains (400 to 600 µm) are placed in a rotating perforated turbomixer. The emplacing of the active principle on the neutral grains is carried out by continuous spraying of the emplacing solution described above, with a support of hot air at a temperature of between 35 and 60°C.

The mass of the active microgranules obtained is sieved through a screen of mesh size ranging from 0.71 to 0.85 mm.

A coating solution is prepared by successively adding Eudragit® RS 30 D (methacrylic acid copolymer), triethyl citrate, talc and Aerosil® R 972 (hydrophobic silica) to the purified water. Stirring of the suspension is maintained until the mixture is homogeneous, and then throughout the coating.

The active microgranules are placed in a rotating perforated turbomixer and continuously sprayed with the coating suspension described above, at a temperature of 30°C. The mass of microgranules obtained

is sieved through a screen of mesh size ranging from 0.8 to 1 mm.

This step can be repeated one or more times. The granules are then lubricated with an amount of talc which is equivalent to 0.5% of the coated mass obtained.

The microgranules obtained have the following composition:

	Batch A	
	Amount mg	**% by mass**
Morphine sulphate	12.5	37.3
Neutral grains	12.5	37.3
Pharmacoat 603®	4.4	13.0
Eudragit RS 30 D®	2.7	8.2
Triethylcitrate	0.5	1.6
Talc	0.7	2.1
Aerosil R972®	0.1	0.4
Content (mg/g)	371	

- **In vitro dissolution tests**

The previously obtained microgranules are dissolved in 500 ml of water at 37°C in a machine with paddles revolving at 100 revolutions/min. The U.V. absorbance reading is measured at two wavelengths, 285 nm and 310 nm.

	Batch A											
Time (hours)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**	**20**
Percentage of dissolution	6.6	20.8	38.8	55.8	69.9	79.9	86.3	90.7	93.2	94.8	97.8	98.3

The in vitro dissolution profile of Batch A is represented by Curve 3 of the figure.

- **Tests for stability of the gelatin capsules of microgranules (Batch A1)**

The stability properties of the microgranules which have been previously obtained and packaged in size 3 gelatin capsules each containing 60 mg of morphine sulphate are measured under storage conditions of at 25°C and 60% relative humidity, for 24 months.

It is observed that the water content of the microgranules is stable at 6% on average, that the appearance of the gelatin capsules is satisfactory and that the active principle titre is in compliance and homogeneous.

The dissolution profiles are fairly stable over time.

After 24 months, the content of pseudomorphine and ampomorphine impurities is in compliance with standards (i.e. less than 05%).

The stability of the same gelatin capsules is also studied for 6 months at 40°C and 75% relative humidity.

It is observed that the active principle titre is in compliance and homogeneous. The dissolution is stable at 6 months. Moreover, the water content is stable.

The stability results are presented in the following tables.

Percentage of dissolution in vitro (Batch A1) Storage conditions 25°C, 60% RH								
Hours	**T0**	**1M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**
1	7.8	7.4	7.7	7.1	6.1	6.5	6.4	5.5
2	21.6	21.9	23.2	22.4	18.9	19.7	20.1	17.0
4	55.2	57.3	60.2	58.1	52.7	53.1	52.9	50.6
6	78.9	81.7	83.7	81.0	77.8	76.1	73.4	76.1
8	89.9	93.4	93.8	90.8	90.1	86.7	81.9	88.5
12	96.0	100.2	98.8	95.9	97.5	93.0	86.2	95.4
16	96.4	100.6	99.8	96.9	98.7	94.6	86.9	95.4

Percentage of dissolution in vitro (Batch A1) Storage conditions 40°C, 75% RH					
Hours	**T0**	**1M**	**2M**	**3M**	**6M**
1	7.8	6.0	5.9	6.1	6.3
2	21.6	19.8	19.7	19.7	21.0
4	55.2	57.1	57.3	57.0	58.7
6	78.9	83.1	81.8	81.9	83.2
8	89.9	94.3	92.1	92.9	94.0
12	96.0	100.1	97.5	98.7	100.3
16	96.4	101.5	98.0	99.6	102.4

		Active principle content (Batch A1)								
		T0	**1M**	**2M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**
25°C, 60% RH	mg/gelatin capsule	59.0	58.4	-	56.7	59.3	58.1	58.0	57.6	57.0
	Variation in %	-	-1.0	-	-3.9	0.5	-1.5	-1.7	-2.4	-3.4
40°C, 75% RH	mg/gelatin capsule	59.0	57.4	58.7	57.5	58.4	-	-	-	-
	Variation in %	0	2.7	-0.5	-2.5	-1.0	-	-	-	-

	Water content (Karl Fisher) (Batch A1)								
	T0	**1M**	**2M**	**3M**	**6M**	**9M**	**12M**	**18M**	**24M**
25°C, 60% RH	6.1%	5.9%	-	5.9%	6.1%	4.8%	6.1%	6.1%	5.9%
40°C, 75% RH	6.1%	6.6%	6.0%	5.3%	6.8%	-	-	-	-

- **Pharmacokinetic study No. 1.**

The bioavailability of gelatin capsules of Batch A1 is compared to that of a reference morphine formulation (containing a dose of 30 mg), after 7-day repeated dose administration in 24 healthy volunteers.

	Plasmatic concentration of			
	morphine		6(glucuronide) morphine	
	Gelatine capsules of microgranules (Batch A1) 60 mg	Reference (Batch S 1079) 30 mg	Gelatin capsules of microgranules (Batch A1) 60 mg	Reference (Batch S 1079) 30 mg
C_{max} (ng/ml)*	18.3	12.8	77.6	59.2
C_{min} (ng/ml)**	7.9	6.8	31.0	30.4
T_{max} (h)*	5	5	6	3

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It is noticed that at Day 7, the plasmatic concentrations of morphine from the gelatin capsules of the invention at 24 hours are higher than the plasmatic concentrations from the reference at 12 hours (+ 1.1 ng/ml), which is a sign of good cover over 24 hours.

- **Pharmacokinetic study No. 2**

The bioavailability of gelatin capsules of Batch A1 is compared to that of a reference morphine formulation, after administration of a single dose of 60 mg in healthy volunteers.

The gelatin capsules of Batch A2 are of size 3 and contain a dose of 60 mg of morphine sulphate per gelatin capsule.

	Plasmatic concentration of			
	morphine		6(glucuronide) morphine	
	Gelatine capsules of microgranules of the invention (Batch A2)	Reference of the prior art (Batch S 1055)	Gelatin capsules of microgranules of the invention (Batch A2)	Reference of the prior art (Batch S 1055)
C_{max} (ng/ml)*	6.97	13.16	64.0	114.8
C_{min} (ng/ml)**	6.0	2.0	5.0	3.0
T_{max} (h)*	218.9	186.9	1471.49	1536.5

* means
** medians

The formulation of the invention and the reference are bioequivalent over the area under the curve parameters, which demonstrates an equivalent absorption of both products. Conversely, the release profile of the formulation of the invention appears more delayed than the reference, with a later T_{max} and a lower C_{max}.

Example 2 (Batches B, C and D)

- **Preparation of the granules**

Granules of the following composition are prepared according to the protocol of Example 1.

	Batch B		Batch C		Batch D	
	Amount (kg)	% by mass	Amount (kg)	% by mass	Amount (kg)	% by mass
Morphine sulphate	13.7	35.1	31.0	40.9	728.8	41.9
Neutral grains	15.4	39.7	26.0	34.3	573.7	33.0
Pharmacoat 603®	4.8	12.3	10.8	14.3	204.1	11.7
PEG 4000	-	-	-	-	51.0	2.9
Eudragit RS 30 D®	3.2	8.2	5.1	6.7	126.5	7.3
Triethylcitrate	0.6	1.6	1.0	1.3	24.9	1.4
Talc	1.0	2.6	1.7	2.2	24.9	1.4
Aerosil®	0.1	0.40	0.2	0.3	6.2	0.4
Content (mg/g)	371.3		368.5		397.9	

Batch B is prepared as in Example 1 in a Glatt perforated turbomixer, whereas Batches C and D are respectively prepared in an O'Hara perforated turbomixer or in a Laf Huttlin.

Tests for in vitro dissolution of the microgranules

Time (h)		1	2	3	4	5	6	7	8	9	10	15	20	24
% of dissolution	Batch B	11.0	29.0	46.2	60.4	71.5	79.9	86.0	90.3	93.4	95.5	98.7	-	-
	Batch C	5.3	22.2	42.1	58.5	71.6	81.6	88.5	93.0	95.9	97.8	100.4	-	-
	Batch D	7.1	20.2	34.8	47.9	58.7	67.4	74.5	80.2	85.0	88.7	97	99.6	100.5

The in vitro dissolution profiles of Batches B, C and D are represented by curves 2, 1 and 4, respectively, of the figure.

- **Tests for dissolution of the gelatin capsules of microgranules**

The gelatin capsules of Batches B2, B1, D1 and C1 contain a dose of 60 mg of morphine sulphate.

Time (h)		1	2	3	4	5	6	8	10	12	14
% dissolution	Batch B1	15.2	34.1	51.1	64.8	75.3	83.2	93.3	-	100.4	-
	Batch C1	6.5	24.1	-	60.3	-	81.9	92.2	96.3	97.4	98.5

- **Tests for stability at 25°C, 60% RH of gelatin capsule Batch B2 (microgranules of Batch B)**

	T0	15D	1M	2M	3M	6M
Water content (%)	-	5.50%	6.00%	6.16%	6.00%	6.02%
Dissolution (hours)						
1	21.2	19.2	14.7	6.9	15.6	16.6
2	45.1	43.1	29.5	22.1	35.7	37.9
3	63.5	62.0	42.9	36.7	53.3	55.8
4	76.1	75.7	54.4	49.4	67.1	69.3
5	85.2	85.2	64.0	60.1	77.3	79.3
6	91.3	91.6	71.9	68.8	84.8	86.5
7	95.5	95.7	78.2	76.0	90.3	91.5
8	98.2	98.4	83.6	81.5	94.1	95.0
12	102.2	102.9	96.3	93.1	101.2	101.0

- **Tests for stability at 40°C, 75% RH of gelatin capsules Batch D1 (microgranules of Batch D)**

	T0	15D	1M	2M	3M	6M
Water content (%)	6.19%	6.40%	6.29%	6.20%	6.30%	6.38%
Dissolution (hours)						
1	11.8	11.9	12.2	12.6	11.6	12.5
2	28.7	28.7	31.0	33.1	31.6	34.3
3	45.8	45.2	48.1	50.6	49.1	51.8
4	59.3	58.4	61.2	63.9	62.5	64.9
5	69.8	68.8	71.5	74.1	72.8	75.2
6	77.9	77.1	79.6	82.1	80.7	83.0
8	88.5	88.8	90.3	91.9	90.8	88.7
10	94.2	95.5	95.4	96.0	95.0	95.7
12	97	98.7	97.6	97.5	96.7	97.1

CLAIMS

1. Sustained-release morphine sulphate microgranules each comprising a neutral support grain coated with an active layer and with a sustained-release layer, characterized in that the sustained-release layer contains a copolymer of methacrylic acid and of methyl methacrylate ester, the relative proportion of the free carboxyl groups and of the ester groups of which is equal to 0.5 approximately, and a silica exhibiting a hydrophobic character.

2. Microgranules according to Claim 1, characterized in that the hydrophobic silica represents from 0.2 to 1% by weight of the microgranules.

3. Microgranules according to one of the preceding claims, characterized in that the acrylic copolymer represents advantageously 5 to 15% by weight of the microgranules.

4. Microgranules according to one of Claims 1 to 3, characterized in that the neutral support grain coated with the active layer contains 40% to 50% of morphine sulphate and 10 to 20% of a pharmaceutically acceptable binder.

5. Microgranules according to one of Claims 1 to 4, characterized in that the sustained-release layer contains a plasticizer such as triethylcitrate and a lubricant.

6. Microgranules according to Claims 4 and 5, characterized in that their composition is as follows:

Morphine sulphate	30 - 40 %
Neutral support grain	30 - 40 %
Binder	10 - 20 %
Methacrylic acid copolymer	5 - 15 %
Plasticizer	1 - 2.5 %
Lubricant	2 - 4 %
Hydrophobic silica	0.2- 1 %

7. Microgranules according to one of the preceding claims, characterized in that the relative mass

proportion of the morphine sulphate and of the neutral support grain is between 40/60 and 60/40.

8. Microgranules according to one of the preceding claims, characterized in that the morphine sulphate represents 30 to 40% by mass of the microgranules.

9. Process for preparing the microgranules according to one of Claims 1 to 8, characterized in that the active layer and the sustained-release layer are applied onto the neutral grains by emplacing in aqueous solution.

10. Pharmaceutical composition containing the microgranules according to one of Claims 1 to 8 optionally obtained according to the process of Claim 9.

PATENT

Title: "Morphine sulphate microgranules, preparation process and composition containing them"

Applicant: LABORATOIRES DES PRODUITS ETHIQUES ETHYPHARM

ABSTRACT

The present invention concerns a novel sustained-release oral formulation of morphine sulphate in the form of microgranules.

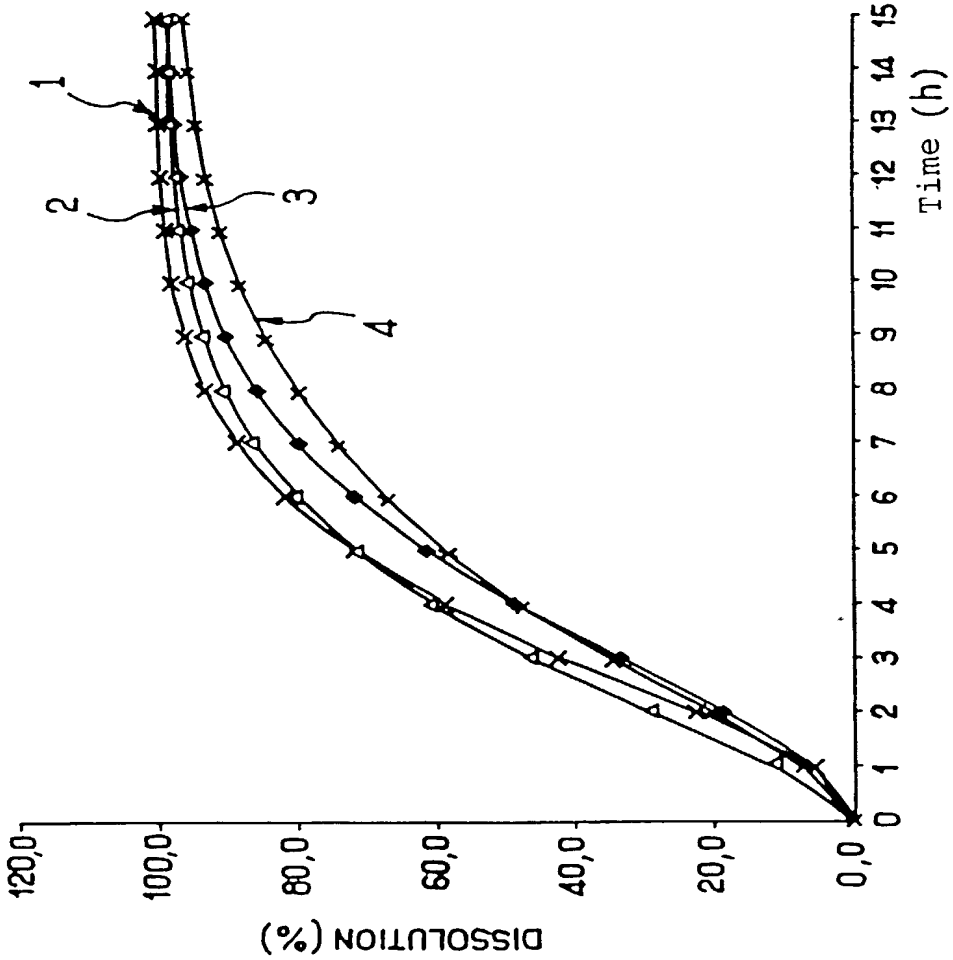
Each microgranule comprises a neutral support grain coated with an active layer and with a sustained-release layer, characterized in that the sustained-release layer contains a copolymer of methacrylic acid and of methyl methacrylate ester, the relative proportion of the free carboxyl groups and of the ester groups of which is equal to 0.5 approximately, and a silica exhibiting a hydrophobic character.

The present invention also concerns a process for preparing these microgranules which is carried out entirely in aqueous medium by emplacing on neutral support grains.

Title: MORPHINE SULFATE MICROGRANULES, METHOD FOR PREPARING SAME AND COMPOSITIONS CONTAINING SAME
Inventor(s) Dominique MARECHAL et al
Attorney Docket No. 065691-0261

10/009341

Only fig.



DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

MORPHINE SULFATE MICROGRANULES, PREPARATION PROCESS AND COMPOSITIONS CONTAINING THEM

the specification of which is attached hereto unless the following box is checked:

☒ was filed on December 10, 2001 as United States Application Number or ~~PCT International Application~~ Number 10/009,341 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
FR99 07259	FRANCE	09/06/99	YES

I hereby claim the benefit under Title 35, United States Code § 119(c) of any United States provisional application(s) listed below.

APPLICATION NO.	FILING DATE

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is known by me to be material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS: PATENTED, PENDING, ABANDONED
PCT/FR00/01573	June 8, 2000	Pending

(19) I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Stephen A. Bent, Reg. No. 29,768; David A. Blumenthal, Reg. No. 26,257; William T. Ellis, Reg. No. 26,874; John J. Feldhaus, Reg. No. 28,822; Patricia D. Granados, Reg. No. 33,683; John P. Isacson, Reg. No. 33,715; Donald D. Jeffery, Reg. No. 19,980; Eugene M. Lee, Reg. No. 32,039; Richard Linn, Reg. No. 25,144; Peter G. Mack, Reg. No. 26,001; Brian J. McNamara, Reg. No. 32,789; Sybil Meloy, Reg. No. 22,749; George E. Quillin, Reg. No. 32,792; Colin G. Sandercock, Reg. No. 31,298; Bernhard D. Saxe, Reg. No. 28,665; Charles F. Schill, Reg. No. 27,590; Richard L. Schwaab, Reg. No. 25,479; Arthur Schwartz, Reg. No. 22,115; Harold C. Wegner, Reg. No. 25,258.

10003551-061902 Docket No.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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